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原　　著

# Clinical Study of Carcinoma of the Gallbladder during the Past 10 Years

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## Introduction

Despite the development of imaging techniques including abdominal ultrasonography, the early diagnosis of carcinoma of the gallbladder remains difficult, the onset of jaundice being a clue to detection of the cancer in many cases. In addition, the definition of early carcinoma of the gallbladder is still controversial.[1,13].

In the surgical treatment of this cancer, there are no standardized surgical procedures according to the nature and degree of extension of cancer necessitating each hospital to develop its own procedures. Such a situation is reflected in the low 5-year survival rate of 26.7%[5], indicating that carcinoma of the gallbladder is one of the worst cancers of organs.

We carried out a retrospective clinical analysis of 31 cases of carcinoma of the gallbladder treated at our department during the past 10 years.

## Subjects and Methods

The subjects were 31 patients who were diagnosed as having carcinoma of the gallbladder based on the findings of pathological examination or imaging at Second Department of Surgery, Kinki University School of Medicine, during the 10 years between April 1977 and March 1987. They ranged in age between 45 and 88 years, with a mean of 64.4, and consisted of 10 males (32%) and 21 females (68%). Laparotomy was performed in 27 of the 31 patients.

These cases were classified according to the 1981 General Rules for Surgical Studies on Cancej of Biliary Tract (Japanese Biliary Surgical Society) for comparison of surgical results on the basis of the cumulative and survival rates and mean survival period. The surgical procedures included resection of the hepatic base; the hepatic base was resected in thickness of>5 mm, accompanied by dissection of $R_1$ or $R_2$.

Key words: Primary carcinoma of the gallbladder, Curative resection, Surgical procedure, Reduction surgery, Early carcinoma of the gallbladder.
索引用語：胆嚢癌，治癒切除術，手術術式，減腫瘍手術，早期胆嚢癌.
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## Results

1. Age and Sex Distinction

Three of the 31 patients were in their 40 s, 9 in their 50 s, 7 in their 60 s, 11 in their 70 s and one in her 80 s (Fig. 1).

2. Initial Symptoms

The cases were divided into early (stage I) and advanced (stage II–IV) types for investigation of initial symptoms. In 4 of the 5 early cases, carcinoma of the gallbladder was detected incidentally following abdominal trauma, or as a result of postoperative pathological

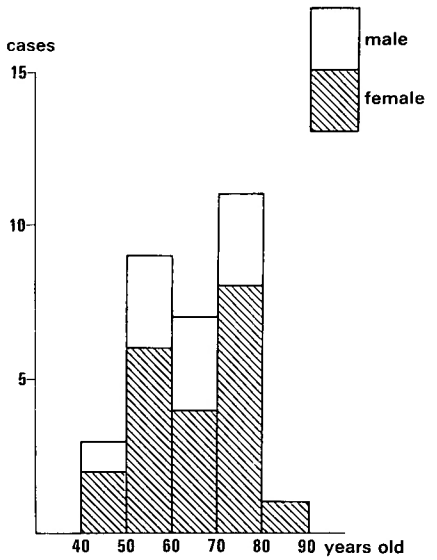


**Fig. 1.** Age and sex of total cases

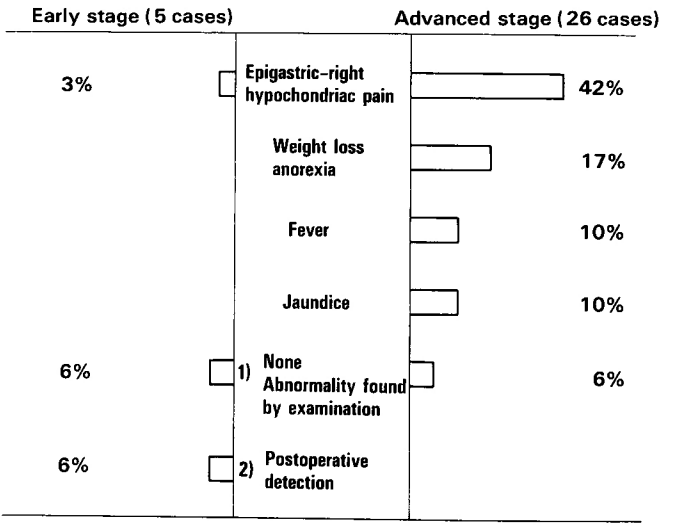


**Fig. 2.** Initial symptoms of 31 cases with carcinoma of the gallbladder

**Table 1.** Association with Cholelithiasis

| | Cases | Cholelithiasis | Complication rate | Unknown |
|---|---|---|---|---|
| Early stage (Stage I) | 5 | 2 | 40% | 0 |
| Advanced stage (Stage II～IV) | 26 | 7 | 27% | 9 |
| Total | 31 | 9 | 29% | 9 |

examination following surgery for cholelithiasis, with no initial symptom. In the advanced group, the initial symptoms were epigastric or right hypochondriac pain in 42%, accompanied by weight loss with anorexia, fever and jaundice, which were not observed in the early group, in 17%, 10% and 10%, respectively (Fig. 2).

3. Association with Cholelithiasis

Associated cholelithiasis was found in 9 (29%) of the 31 cases. These 9 cases were also divided into early and advanced groups for analysis. Two (40%) of the 5 early cases and 7 (27%) of the 26 advanced cases, were associated with cholelithiasis with no significant difference by the chi-square test (Table 1).

4. Stage Classification and Therapeutic Methods

The cases were staged according to the histological stage classification in the General Rules for Surgical Studies on Cancer of Biliary Tract. Five cases (16%) were in Stage I, 2 (8%) in stage III and 24 (76%) in stage IV, with no stage II case (0%).

According to the therapeutic procedure, curative resection was achieved in all of the 5 stage I and both of the 2 stage III patients. However, curative resection was not possible in any of the 24 stage IV patients, 13 of whom underwent non-curative resection, 7 no resection and 4 no surgery. Two of the 4 patients who did not undergo surgery were treated by percutaneous transhepatic cholangiodrainage, and one by immunochemotherapy alone. The remaining one patient received no treatment. Resection was achieved in 65% (20 patients): curative resection in 23% (7) and non-curative resection in 42% (13). No resection was possible in 23% (7), and 12% (4) did not undergo surgery (Table 2).

5. Surgical Procedure

Table 3 shows the surgical procedures used. Five of the 7 patients undergoing curative resection were in stage I: 3 received cystectomy alone and 2 cystectomy+dissection of $R_1$.

**Table 2.** Classification of stage of carcinoma of the gallbladder

| | Cases | Curative resection | Non-curative resection | No resection | Inoperation |
|---|---|---|---|---|---|
| Stage I | 5( 16) | 5 | 0 | 0 | 0 |
| II | 0( 0) | 0 | 0 | 0 | 0 |
| III | 2( 8) | 2 | 0 | 0 | 0 |
| IV | 24( 76) | 0 | 13 | 7 | 4 |
| Total | 31(100) | 7(23) | 13(42) | 7(23) | 4(12) |

(%)

**Table 3.** Surgical procedure of carcinoma of the gallbladder

| | | Surgical procedure | cases |
|---|---|---|---|
| Curative resection (7 cases) | Stage I | Cystectomy alone | 3 |
| | | Cystectomy + $R_1$ | 2 |
| | Stage III | Cystectomy + $R_1$ | 1 |
| | | Cystectomy + resection of hepatic base | 1 |
| Non-curative resection (13 cases) | Stage III | Cystectomy + resection of hepatic base | 4 |
| | | Cystectomy alone | 3 |
| | | Cystectomy + choledochojejunostomy | 2 |
| | | Cystectomy + $R_1$ | 1 |
| | | Cystectomy + pylorogastrectomy | 1 |
| | | Cystectomy + transverse colectomy | 1 |
| | | Cystectomy + resection of the right Posteroinferior segment of the liver | 1 |
| No resection (7 cases) | Stage IV | Choledochostomy | 2 |
| | | Choledochojejunostomy | 2 |
| | | Gastrojejunostomy | 1 |
| | | Gastrojejunostomy + tubing in the hepatic artery | 1 |
| | | Exploratory laparatomy | 1 |

The remaining 2 were in stage III, undergoing cystectomy+dissection of $R_1$ and cystectomy +resection of the hepatic base, respectively.

Cancers were in stage IV in all of the patients undergoing non-curative resection: cystectomy+resection of the hepatic base in 4, cystectomy alone in 3, cystectomy+dissection of $R_1$ in one. Cystectomy was combined with choledochojejunostomy in 2 patients and with pylorogastrectomy, transverse colectomy and resection of the right posteroinferior segment of the liver in one each.

Two each of the 7 unresected patients were treated by choledochostomy and choledochojejunostomy, and one each, by gastrojejunostomy, gastrojejunostomy+tubing in the hepatic artery and exploratory laparotomy.

6. Prognosis

The one-year survival rate, mean survival period and longest survival period were calculated according to the therapeutic proceduce (Table 4).

The overall one-year survival rate was 34.6%. The one-year survival rates for the curatively resected, non-curatively resected and unresected patients and the patients undergoing no surgery were 83.3%, 36.4%, 0% and 0%, respectively.

The mean survival period was $24.3\pm10.9$, $8.5\pm3.0$, $1.9\pm0.6$ and $3.3\pm2.6$ mos., respectively, in these groups. Wilcoxon's t-test revealed significant differences in the mean survival period between the curatively resected group and the groups undergoing non-curative resection, no resection or no surgery ($P<0.05$). However, there was no significant difference between the non-curatively resected and unresected groups, or between the unresected and

**Table 4.** One-year survival rate and mean survival period and longest survival period

| | One-year survival rate | Mean survival period (mos.) | Longest survival period (mos.) |
|---|---|---|---|
| Curative resection (7 cases) (5/6 cases) | 83.3% | 24.3±10.9 | Surviving after 7 yrs. 4 mos. |
| Non-curative resection (13 cases) (4/11 cases) | 36.4% | 8.5±3.0* | Died 2 yrs. 9 mos. later. |
| No resection (7 cases) (0/5 cases) | 0% | 1.9±0.6* | Died 4 mos. later. |
| Inoperation (4 cases) (0/4 cases) | 0% | 3.3±2.6* | Died 11 mos. later. (untreated) |
| Total (31 cases) (9/26 cases) | 34.6% | | |

M±SD, *P<0.05 (as compared to curative resection) ( ): cases

non-surgical groups. These results indicate that despite resection of major tumors, no prognostic improvement was attained in the non curatively resected patients.

The longest survival period was 7 yrs. and 4 mos. (the patient surviving), 2 yrs. and 9 oms., 4 mos. and 11 mos., respectively, in the curatively resected, non-curatively resected, unresected and non-surgical groups.

Two (7%) of the 27 unresected patients died as a direct result of surgery, both of whom had undergone choledochostomy alone.

7. Cumulative Survival Rate

Statistical analysis by Kaplan-Meier's method revealed a significant differences between the cumulative survival rates for stage I and IV ($P<0.05$). The one-year cumulative survival

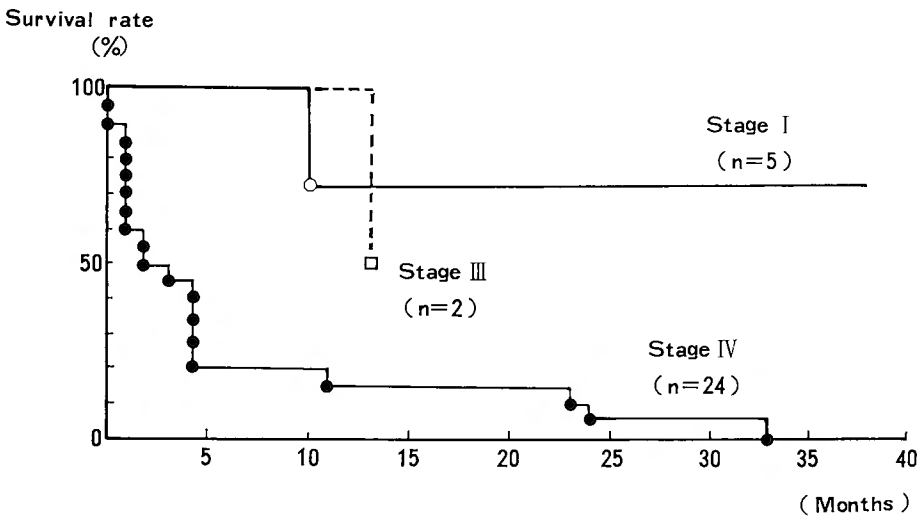


**Fig. 3.** Survival rate and staging

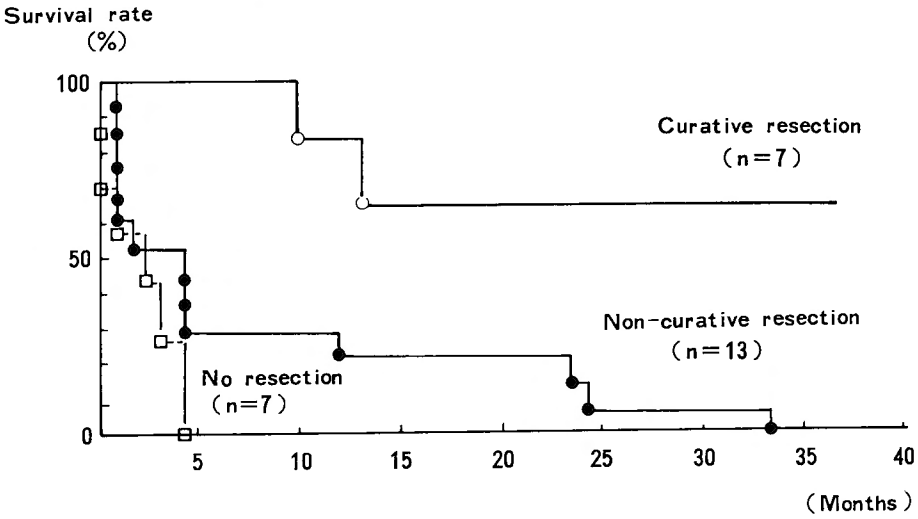


**Fig. 4.** Survival rate of each treatment

rate for stage I was 75%, and that for stage IV, 17%.

The 3-year cumulative survival rates were 75% and 0%, respectively (Fig. 3). According to the therapeutic procedure, there were significant differences between the curatively resected group and the non-curatively resected group or unresected group ($P<0.05$). The one-year cumulative survival rates associated with curative resection and non-curative resection were 83% and 23%, respectively, and the 3-year cumulative survival rates, 67% and 0% (Fig. 4).

8. Mode of Cancer Extension

The 20 resected cases were analyzed with respect to the mode of extension of carcinoma of the gallbladder observed macroscopically during surgery. Intrahepatic extension and peritoneal serosal infiltration were most frequent, occurring in 11 cases (55%) each. Intrahepatic extension was due to direct invasion in 9 cases (45%) and metastasis in 2 (10%). Metastasis due peritoneal dissemination was found in 4 cases (20%), and lymph node metastasis and invasion of the bile duct in 3 (15%) each (Table 5).

**Table 5.** Mode of Cancer Extension

(20 resected cases)

| Mode of extension | | Cases (%) |
|---|---|---|
| Intrahepatic extension | direct infiltration | 9 (45%) |
| | metastasis | 2 (10%) |
| Serosal (peritoneal) infiltration | | 11 (55%) |
| Metastasis due to peritoneal dissemination | | 4 (20%) |
| Lymph node metastasis | | 3 (15%) |
| Infiltration of the bile duct | | 3 (15%) |

**Table 6.** Investigation of early cases

| Case | Age, Sex | Initial symptom | Preoperative diagnosis | Surgery | Cholelithiasis | Focal region | Depth of invasion | Prognosis |
|---|---|---|---|---|---|---|---|---|
| 1 | 52, Male | Postoperative detection | (−) | Radical surgery for gastric cancer and cystectomy | (−) | Gbf | SS | 7yrs. 4mos. (surviving) |
| 2 | 63, Female | Postoperative detection | Cholelithiasis | Esophageal transection and cystectomy | (+) | Gf | Pm* | 1yrs. 10mos. (surviving) |
| 3 | 53, Female | Traffic accident (Abnormality found by examination) | lesion with protruded gallbladder | cystectomy + $R_1$ | (−) | Gf | SS | 1yrs. 9mos. (surviving) |
| 4 | 47, Female | Abnomality found by examinatin | lesion with protruded gallbladder | cystectomy + $R_1$ | (−) | Gbn | m* | 3mos. (surviving) |
| 5 | 58, Female | Epigastric pain | cholelithiasis | cystectomy | (+) | Gf | Pm* | 10mos. (death) |

* Early carcinoma of the gallbladder (3 cases)

9. Early Cases

The five stage I cases were analyzed (Table 6).

Four of the five patients are surviving and belong to the curatively resected group. Three cases showed early carcinoma of the gallbladder which was definied as "a cancer being localized in the gallbladder, with invasion limited to the subserosa or tunica propria." of these 3 patients, one with pm cancer died at 10 months. Cancers were detected by health checkups or by accident in 4 of the 5 early cases.

## Discussion

Carcinoma of the gallbladder is believed to be prevalent among aged females, with a peak in the 70 s and a mean of age of 62.5 years by PIEHLER et al.[9] or 71.7 years by SHIEH et al[11]. In addition, this cancer is more frequent among females than males, with a male to female ratio of 1 : 3–4[9,12], or that of 1 : 1.7 reported by MAKI et al.[4] in Japan. Our data are similar to these findings: 1 : 2.1 in the male to female ratio and 64.4 years in the mean age.

The most frequent initial symptom was epigastric or right hypochondriac pain (45%), as was reported earlier.[8] Concerning the relationship between the stage of carcinoma of the gallbladder and symptoms, the early cases exhibited no weight loss-anorexia, fever or jaundice, which therefore, proved to be signs of advanced cancer. Chololithiasis was found in 29% of the total series. This rate is lower than 73.9%, 60% and 72%, respectively, reported by PIEHLER et al.[9], MAKI et al.[4] and NAKAYAMA et al.[6] These high rates were probably due to the fact that car-

cinoma of the gallbladder was difficult to detect directly and was incidentally found during the diagnosis and treatment of cholelithiasis in most cases. The rate of association of cholelithiasis was 40% in the early group and 27% in the advanced group, with no significant difference.

Despite the recent remarkable progress in imaging of the biliary system and tumor markers, reports show that with exception of early cases, therapeutic results for carcinoma of the gallbladder are very poor, particularly in advanced cases. However, MIYAZAKI et al.[5] reported 5-year survival rates of 11.1% and 3.2%, respectively, for stages III and IV from their nationwide survey in 1983. Thus, there are now long-term survivors of advanced carcinoma of the gallbladder. However, only one of our patients has survived for more than 5 years, not justifying calculation of the 5-year survival rate. While most of the stage IV patients (20/24, 83%) died within 4 mos, 4 survived for more than one year, with a longest period of 2 yrs. and 9 mos. In all of these 4 patients, choledochojejunostomy, pylorogastrectomy or resection of the right posteroinferior segment of the liver was combined with cystectomy. As well as the reports by MIYAZAKI et al.[5] and KOSUGE et al.[3], these results suggest that the therapeutic results for patients with stage IV cancer, which has been fatal, may improve by more active therapy.

The curative resection rates in most reports are approximately 20%: 19.8% in the 1983 nationwide questionnaire survey[5], 22% by SATO et al.[10] and 18.9% by KAWAGUCHI et al.[2] We observed a similar rate (23%).

The most frequent modes of cancer extension were intrahepatic extension and peritoneal serosal infiltration (55% in both), and these two factors were responsible for non-curative resection in most cases. Therefore, a large area needs to be resected to achieve curative resection.

Prognostic evaluation of our cases indicate that successful curative resection results in fairly satisfactory prognosis (2-year survival at shortest) for carcinoma of the gallbladder that extend mainly regionally, but that unsuccessful curative resection does not lead to prolongation of survival, even if the major focus is resected. In other words, reduction surgery is meaningless. Accordingly, more actively extended surgery is recommended if curative resection appears possible, and a less invasive procedure, if curative resection seems impossible.

Four of the 5 early cases showed no initial symptom, indicating that early detection of this cancer is difficult and calling for further spread of ultrasonography. Three patients had early carcinoma of the gallbladder, and one of them who showed a pm cancer died at 10 months. Autopsy of this patient strongly suggested continuous infiltration of the hepatic base. Only cyestectomy was carried out for this patient who deserved additional resection of the hepatic base. TSUCHIYA et al.[15], NAKAYAMA et al.[7] and TASHIRO et al.[14] recommend resection of the hepatic base and disection of regional lymph nodes (R2) in combination with cystectomy for early carcinoma carcinma of the gallbladder. Thus, active resection of the hepatic base seems necessary.

## Conclusion

Thirty-one cases of carcinoma of the gallbladder treated at our department during the past 10 years were retrospectively analyzed. Successful curative resection resulted in fairly favorable

prognoses, but survival was not prolonged in cases in which curative resection was impossible, even if the major tumor was resected, indicating that reduction surgery was meaningless. Therefore, more actively extended surgery is recommended to achieve curative resection in more cases.

The summary of the present report was presented at the 141st Meeting of Kinki Surgical Society (Osaka) in May 1987 and at the 49th General Meeting of Japanese Society for Clinical Surgery (Fukuoka) in October 1987.

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## 和文抄録

# 胆嚢癌症例の臨床的検討

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1977年4月から1987年3月までの10年間に教室で経験した胆嚢癌症例31例について臨床的検討を加えた．組織学的 Stage 分類では，Stage Ⅰ 5例（16%），Stage Ⅱ，0例（0%），Stage Ⅲ，2例（8%），Stage Ⅳ，24例（76%）であり，進行例が約80%をしめていた．全症例での切除率は65%，そのうち治癒切除率は23%，非治癒切除率42%，非切除率23%，非手術は12%であった．平均生存期間は，治癒切除，非治癒切除，非切除，非手術では，それぞれ24.3±10.9カ月，8.5±3.0カ月，1.9±0.6カ月，3.3±2.6カ月であった．非治癒切除と非切除では統計学的有意差は無く，治癒切除を行いえれば，比較的良好な予後が期待出来るが，治癒切除を行いえなければ，たとえ主腫瘤を切除していても，生命予後は改善されぬ為，より積極的な拡大手術を心掛け，治癒切除症例の増加に努めるべきであると考えられた．